Hyperapobetalipoproteinemia

Plasma Lipoprotein Responses to Oral Fat Load

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To better define lipid transport in patients with hyperapobetalipoproteinemia (HyperapoB), the response to an oral fat load was studied in six normotriglyceridemic patients with the disorder. Plasma triglycerides; Sf > 400, and Sf 20 to 400 triglycerides; Sf > 20 B100; total HDL and HDL subfractions (HDL_2 and HDL_3) were measured serially for a 7-hour period after an oral fat load and changes in these parameters were compared to those observed in six normolipidemic controls. In addition, plasma triglyceride levels and HDL_2 and HDL_3 cholesterol were also determined in seven patients with Type IV hyperlipoproteinemia: three with normal LDL apo B levels and four with HyperapoB. When the two normotriglyceridemic groups were compared, the patients with HyperapoB had significantly higher fasting levels of SF > 400 lipoproteins and higher fasting VLDL and LDL levels than the normal patients. After the fat load, Sf 20 to 400 triglycerides and Sf > 20 B100 levels increased in both groups. Plasma triglycerides rose to a higher level in the HyperapoB patients than in the normal group, but more strikingly, remained elevated in the HyperapoB patients, an elevation due principally to a persistant increase in Sf > 400 triglycerides. On the other hand, HDL_2 cholesterol dropped substantially in the HyperapoB patients but not in the normal patients. Finally, in the hypertriglyceridemic group, after the fat load, HDL_2 cholesterol levels did not change in the patients with normal LDL apo B levels but did decrease in those with elevated plasma LDL apo B.
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Hyperapobetalipoproteinemia (HyperapoB) was first recognized in normocholesterolemic patients with angiographically documented coronary artery disease, and was defined as an increased level of the major apoprotein in low density lipoprotein (LDL) — apo B — where this increase was disproportionate to that of the other moiety of LDL, its cholesterol component.[1] Some hypertriglyceridemic patients also have HyperapoB, and atherosclerosis appears to be more frequent in these than in other individuals with normal plasma LDL apo B levels.[2, 3] We have recently shown that the long-term patency of saphenous vein aortocoronary bypass grafts, as well as the rate of progression of atherosclerosis in native coronary vessels, is related to the serum lipoprotein levels, among which plasma LDL apo B and HDL cholesterol appear to be the most important determinants of outcome.[4]

While our studies, as well as the work of others,[5–11] indicate that plasma LDL apo B may reflect atherogenic risk from low density lipoprotein more clearly than LDL cholesterol, they do not elucidate that metabolic defects responsible for HyperapoB. In this regard, we have shown that the physicochemical bases for the characteristic abnormalities of LDL in this syndrome are due to differences in LDL size and lipid content. That is, just as familial hypercholesterolemia is characterized by a major portion of the LDL particles being cholesterol-enriched, HyperapoB is characterized by most of the LDL particles being denser than normal because they contain less cholesterol and relatively more protein than normal.[12] A similar observation — that LDL in patients with coronary disease has a lower molecular weight than in normal individuals — has recently been reported by Crouse et al.[13]

However, little is known of the other plasma lipoproteins in HyperapoB except that VLDL levels have tended to be higher, and on occasion, fasting HDL_2 levels have been lower than normal.[1, 2, 12, 14] Consequently the present study was designed to document the dynamic responses of the plasma lipoproteins in patients with HyperapoB to an oral fat load and to compare these findings to the responses observed in normal persons.

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Methods

Study Subjects

Nineteen subjects were studied (Table 1). The first group of six patients with normotriglyceridemic HyperapoB all had LDL cholesterol levels less than 200 mg/dl, plasma LDL apo B levels greater than 120 mg/dl, and plasma triglyceride levels less than the 95th percentile as defined in the Lipid Research Clinics (LRC) prevalence study.[15] The men, but not the women, has plasma triglyceride levels under the mean for the LRC prevalence data. In one woman (MH), plasma cholesterol just exceeded the 95th percentile although LDL cholesterol was under it; in another woman (MB), both total and LDL cholesterol levels exceeded the 95th percentile limits. In this group, each man had suffered a documented myocardial infarction with angiographically proven coronary atherosclerosis. One woman (MH) had experienced a myocardial infarction while on oral contraceptives and subsequently had a normal coronary angiogram. None of the patients were on oral contraceptives or lipid-lowering agents at the time of the study and none had hypertension or diabetes. One man (JR) was a smoker; another man (WR) was a former smoker. Clinical data on all subjects are shown in Table 1.

Six controls, all normolipidemic, were selected from the cardiology staff of the hospital. All control subjects were free of clinical coronary artery disease, were nonsmokers, and were not hypertensive or diabetic.

Seven patients (all men) with Type IV hyperlipoproteinemia were studied. All had plasma triglyceride levels greater than the 95th percentile and none had chylomicrons demonstrable after plasma was left standing overnight at 4° C. None had LDL cholesterol levels greater than the 95th percentile of the LRC prevalence study.[15] Three had plasma LDL apo B levels below 120 mg/dl; four had values greater than this. They were divided into two groups: those with normal LDL apo B (three men) and those with HyperapoB (four men). None were taking any lipid-lowering medications. Of the three with normal plasma LDL apo B levels, one was 62 and two were 43 years old. The 62-year-old had chest pains but did not have hemodynamically significant coronary artery lesions at coronary angiography. Of the four with HyperapoB, one was 37, one was 63, one was 45, and one was 66 years of age. All but the last had symptomatic coronary artery disease documented by coronary angiography.

None of the individuals studied had been ill within the preceding 6 months. None had recent weight change and all were consuming a standard North American diet. The study design was reviewed and approved by an Ethics Committee of the Department of Medicine at the Royal Victoria Hospital. All patients gave consent after being informed as to the purpose and nature of the study.

Table 1. Clinical Data and Fasting Lipoprotein Levels

Group	Age	Sex	MBWI	TC	TG	LDL C	LDL B	HDL C	HDL_2 C	HDL_3 C	Sf > 20 B100
Normal											
DM	47	M	25.6	156	96	93	87	44	16	28	3.4
DF	39	M	23.8	146	100	88	71	38	9	28	3.3
AS	42	M	23.0	180	122	119	99	38	13	24	4.4
KC	26	F	22.8	156	80	67	48	83	38	45	5.1
SS	33	F	20.7	168	90	76	66	74	26	48	6.5
HV	34	F	19.1	193	84	91	75	85	22	64	3.1
mean	37		22.5	167	95	89	74	60	21	40	4.3
± SD	7		2.1	16	14	18	16	21	10	16	1.3
Hyperapo B											
WR	46	M	30.0	201	104	111	122	69	21	48	3.4
JR	50	M	26.9	194	118	122	140	48	12	31	7.8
OD	60	M	23.1	185	137	121	123	37	10	27	6.2
MH	48	F	22.3	273	143	176	158	68	22	45	8.2
CD	33	F	23.2	224	142	142	176	54	23	31	5.3
MB	33	F	18.8	265	155	178	195	56	18	38	11.0
mean	45		24.0	224	133	142	152	55	18	37	7.0
± SD	10		3.6	34	17	29	27	11	6	9	2.6
p	NS		NS	<0.05	<0.05	<0.01	<0.05	NS	NS	NS	<0.025
Type IV: normal apo B											
PP	43	M	25.2	360	722	139	98	52	27	25	
JB	43	M	22.8	411	827	138	99	44	16	29	
AB	46	M	24.9	193	399	120	108	46	23	23	
Type IV: HyperapoB											
DS	66	M	27.4	183	285	98	136	28	3	25	
FK	63	M	22.2	232	306	96	149	43	31	12	
KB	37	M	23.3	193	525	100	156	37	20	17	
JG	45	M	24.5	345	441	196	146	61	17	44	

MBWI = mean body weight index; FFA = free fatty acid; TC = total cholesterol; TG = triglyceride; LDL = low density lipoprotein; HDL = high density lipoprotein; C = cholesterol; HyperapoB = hyperapobetalipoproteinemia.

Study Design

All patients fasted for at least 12 hours before the experiment. The lipid meal consisted of 350 ml of heavy whipping cream mixed with one tablespoon of granulated sugar and one tablespoon of instant dry nonfat milk. This provided 1362 kcal, of which (by weight) 5.1% was protein, 25.6% carbohydrate, and 69.3% fat (130 g). The total amount of cholesterol was 480 mg, and the polyunsaturated-to-saturated fatty acid ratio was 0.059.[16] The volume administered was standardized for body surface area (BSA) — the amount above given per 2.5 m^2 BSA. The patients were ambulatory but were not allowed food or liquid except for water during the study. The fat meal was ingested within 5 minutes and was well tolerated by all subjects.

The studies lasted 7 hours. Blood was drawn at 0, 2, 2.5, 3, 3.5, 4, 5, 6, and 7 hours, and was collected in 7 ml tubes containing EDTA (1 mg/ml). Plasma was separated by centrifugation at 2500 *g* at 4° C, and on each sample, the following parameters were assayed: total triglycerides, cholesterol, Sf > 400 triglycerides, Sf 20 to 400 triglycerides, and Sf > 20 apo B 100. High density lipoprotein (HDL) cholesterol and its subfractions, HDL_3 and HDL_2 cholesterol, were measured at 0, 3, 5, and 7 hours.

Plasma triglycerides and cholesterol were measured enzymatically. Sf > 400 lipoproteins (chylomicrons) were then isolated from plasma. To do so, 2 ml of fresh plasma was layered under 10 ml of d = 1.006 saline in a 12.5 ml quick-seal tube. The sample was spun in a 50 Ti rotor at 40,000 rpm for 30 minutes.[17] The supernatant fluid was collected in approximately the top 3.5 ml by tube slicing. The infranatant fluid was then adjusted to a volume of 8.5 ml with a density of 1.006 g/ml in a polycarbonate ultracentrifuge tube. The sample was centrifuged in a Ti 50 rotor at 40,000 rpm for 18 hours. The Sf 20 to 400 lipoproteins were collected in approximately the top 2.5 ml by aspiration. LDL cholesterol was estimated as plasma cholesterol — (VLDL cholesterol + HDL cholesterol). LDL apo B was measured by radial immunodiffusion;[18] Sf > 20 B100 was measured by radioimmunoassay using a monoclonal antibody (4G3) that reacted with B100 but not B48.[19] HDL cholesterol was measured by heparin manganese precipitation,[20] and HDL_2 and HDL_3 cholesterol was estimated as described by Gidez.[21] The mean body weight index was calculated for each patient as weight (kg) divided by height^2 (meters).

Fasting values in the first two groups were compared by nonpaired *t* test. In these groups, two points during the test were selected for comparison: these were the point at which there was the greatest change from the fasting value (peak value) and the final point in the test (final value), the 7-hour point. Peak values were selected to take into account temporal differences in response among subjects. Peak and final values were compared within each group by paired *t* test. Peak change (the difference between peak value and fasting) and final change (the difference between final value and fasting) were calculated for each parameter in both groups. Because fasting values often differed between the two groups, absolute values were not compared, but, rather, the peak and final changes were compared in order to normalize the fasting differences. These comparisons were carried out by nonpaired *t* test.

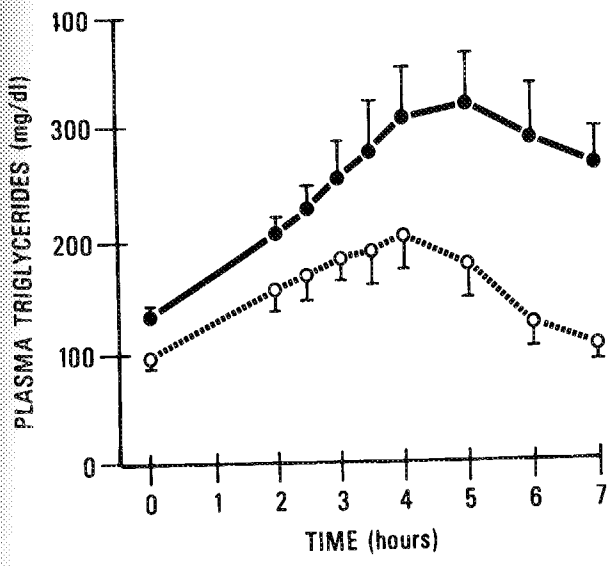

Figure 1. Serial changes and plasma triglycerides following an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

Results

The results will be presented first for the two normotriglyceridemic groups, that is, the controls and the normotriglyceridemic patients with HyperapoB. The clinical data and fasting plasma lipoprotein levels for both these groups are given in Table 1. These two groups differ, with Sf > 400 and VLDL and LDL levels being significantly higher in the HyperapoB group than in the normal group, although HDL, both total and subclasses, did not differ significantly. The control group was younger than the HyperapoB group although their mean body weight index was virtually the same.

Plasma Triglycerides

The sequential changes in plasma triglycerides are shown in Figure 1. The peak and final values for this and subsequent parameters are shown in Table 2, while the peak and final changes are shown in Table 3. In the normal group, plasma triglycerides rose to a maximum at 4 hours, thereafter declining rapidly to fasting levels. In both groups, as expected, postabsorptive peak triglyceride levels were significantly higher than fasting levels. The peak increase, however, was significantly greater in the HyperapoB group than in the normal group. Moreover, the final value in the normal group did not differ significantly from the fasting value. By contrast, in the HyperapoB group, plasma triglycerides at 7 hours were double the fasting level, with the 7-hour difference from fasting much larger in the HyperapoB group than in the normal group (134 ± 60 vs 8 ± 31 mg/dl, $p < 0.005$).

Sf > 400 Triglycerides

The changes in the triglyceride-rich lipoproteins separated by ultracentrifugation are shown in greater detail in

Table 2. Peak and Final Lipoprotein Values Following an Oral Fat Load

Lipoprotein		Peak value	p^*	Final value	p^*
Plasma Tg	N	220±80	<0.005	103±33	NS
	HB	346±116	<0.005	264±74	<0.005
Sf > 400 Tg	N	112±62	<0.01	28±21	NS
	HB	195±119	<0.01	105±70	<0.025
Sf 20–400 Tg	N	78±16	<0.01	28±10	<0.05
	HB	83±20	<0.0025	65±24	NS
Sf > 20 B 100	N	7.6±2	<0.01	4±0.9	NS
	HB	11±3.5	<0.005	8.7±4.9	NS
HDL C	N	60±15	NS	59±14	NS
	HB	46±5	<0.025	50±7	<0.025
HDL_2 C	N	17±12	NS	17±11	NS
	HB	3±3	<0.005	3±4	<0.005
HDL_3 C	N	42±15	NS	42±17	NS
	HB	45±10	<0.01	45±10	<0.01

*Peak and final value compared to fasting.
N = normal; HB = hyperapobetalipoproteinemia; Tg = triglyceride; C = cholesterol.

Table 3. Peak and Final Change in Lipoproteins Following an Oral Fat Load

Lipoprotein		Peak change	p^*	Final change	p^*
Plasma Tg	N	124±73	<0.05	8±31	<0.005
	HB	213±112		134±60	
Sf > 400 Tg	N	95±60	NS	11±16	<0.025
	HB	165±112		73±64	
Sf 20–400 Tg	N	21±13	<0.025	−8±6	<0.005
	HB	39±18		22±22	
Sf > 20 B100	N	3.3±2.2	NS	−0.4±1.4	NS
	HB	4.1±2.4		1.7±3.1	
HDL C	N	−1±18	NS	−1±14	NS
	HB	−6±11		−9±7	
HDL_2 C	N	−9±8	NS	−4±13	<0.05
	HB	−15±7		−17±6	
HDL_3 C	N	2±12	NS	2±7	NS
	HB	9±6		9±6	

*Nonpaired *t* test comparing between group changes.
N = normal; HB = hyperapobetalipoproteinemia; Tg = triglyceride; C = cholesterol.

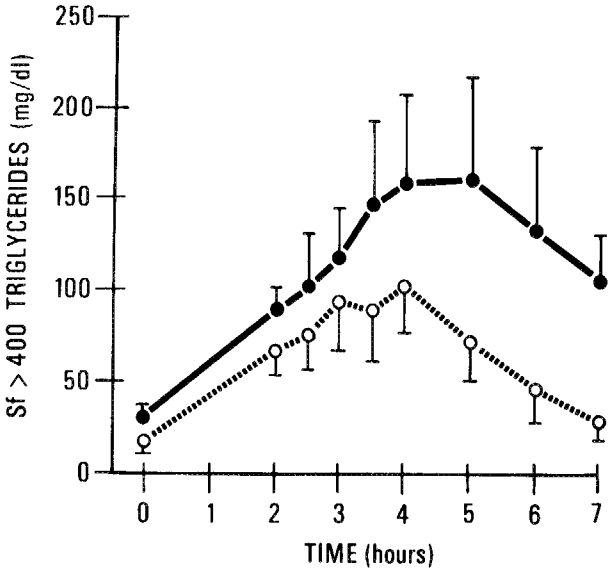

Figure 2. Sf > 400 triglycerides after an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

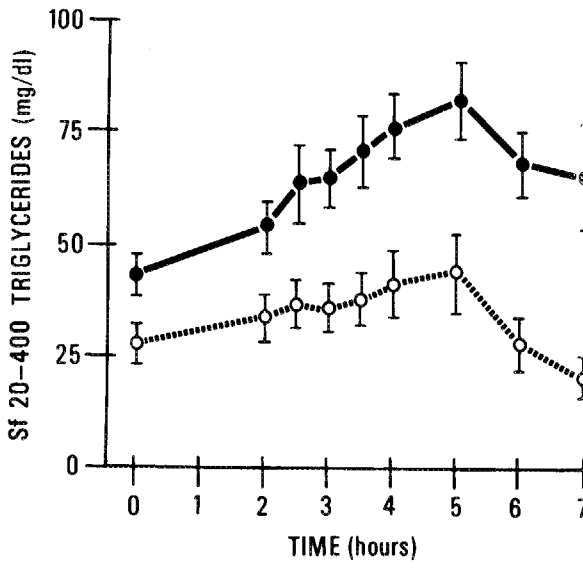

Figure 3. Sf 20 to 400 triglycerides after an oral fat load. ○ normal patients; ● = patients with hyperapobetalipoproteinemi

Figures 2 to 4 and Tables 2 and 3. First, note that the SF > 400 triglyceride levels were significantly higher even after fasting in the HyperapoB group (31 ± 9 vs 17 ± 9 mg/dl, $p < 0.01$). After the fat load, the Sf > 400 triglycerides rose substantially in both groups to maximum and, in fact, the peak change from fasting did not differ significantly between the two groups. At 7 hours in the normal group, the Sf > 400 triglycerides had returned to fasting levels but in the HyperapoB group, the levels were significantly higher (105 ± 70 mg/dl vs 28 ± 21 mg/dl, $p < 0.025$). Further, the difference from fasting (final change) at 7 hours was significantly greater in the HyperapoB group than in the normal group (73 ± 64 vs 11 ± 16 mg/dl, $p < 0.025$).

Sf 20–400 Triglycerides and Sf > 20 B100

In both groups, Sf 20–400 triglycerides rose significantly during the fat meal, with the peak and final changes from fasting being significantly greater in the HyperapoB group than in the normal group. In addition, the changes in Sf > 20 B100 are of interest. As expected, the fasting levels were significantly higher in the HyperapoB group. During the postprandial period, however, peak levels rose significantly in both groups. In the normal groups, Sf > 20 B100 appeared to increase and return to baseline. No regular pattern was obvious in the HyperapoB group, and there was considerable oscillation of the mean values.

High Density Lipoprotein

In the normal group, HDL cholesterol changed little throughout the test period (Tables 2 and 3, Figure 5). Further, in this group, neither HDL_3 nor HDL_2 cholesterol changed significantly (Figures 6 and 7). The peak change values did demonstrate a decrease in the mean HDL_2 cholesterol value, but this was not statistically significant. In the HyperapoB group, on the other hand, the outcome differed. Total HDL cholesterol did decrease significantly (Tables 2 and 3) and this was due to a balance between a

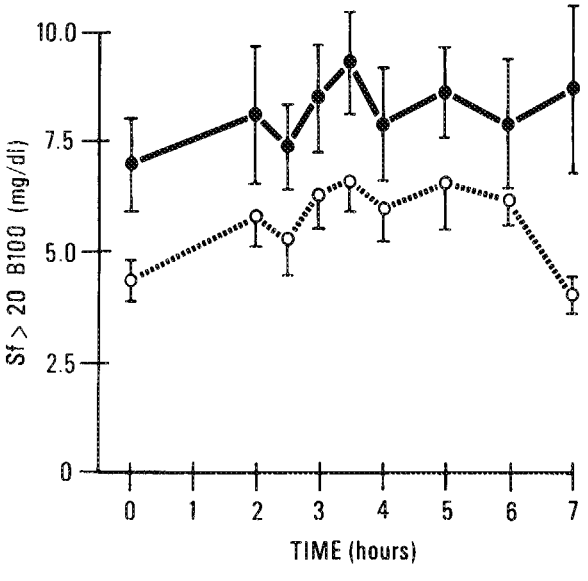

Figure 4. Sf > 20 B100 after an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

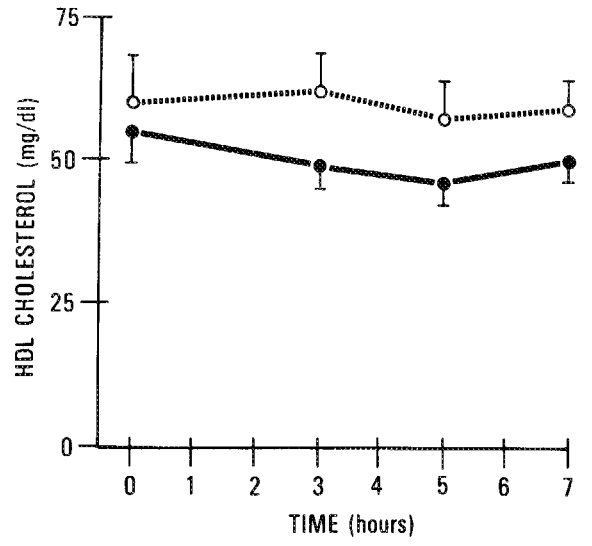

Figure 5. HDL cholesterol after an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

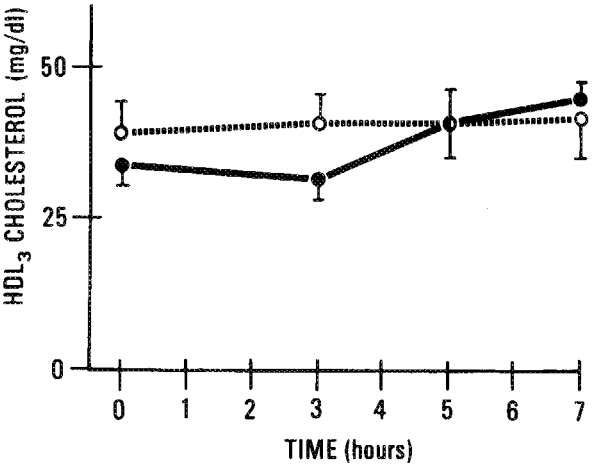

Figure 6. HDL_3 cholesterol after an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

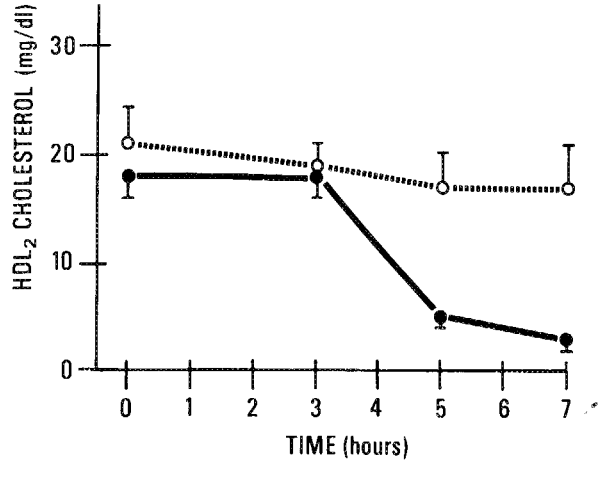

Figure 7. HDL_2 cholesterol after an oral fat load. ○ = normal patients; ● = patients with hyperapobetalipoproteinemia.

very sharp decrease in HDL_2 cholesterol and a slight, but statistically significant, increase in HDL_3 cholesterol.

Results in Type IV Hyperlipoproteinemia

Seven patients with Type IV hyperlipoproteinemia were studied: three with normal plasma LDL apo B levels and four with elevated plasma LDL apo B. Their fasting values are given in Table 1 and the response to the fat load is shown in Figure 8. In both groups, plasma triglycerides rose after the fat load and remained above the fasting level throughout the study period. The changes in HDL cholesterol subfractions were of interest. In both groups, just as in the controls, HDL_3 cholesterol changed little during the test. In the Type IV normal apo B group, as in the normolipidemic normal apo B group, HDL_2 cholesterol changed little, whereas in the type IV HyperapoB group it decreased in three of the four patients while in the fourth, even at the onset, HDL_2 cholesterol was low.

Discussion

As has already been noted repeatedly,[16, 22–24] we also observed that normal individuals dispose of a fat load very effectively, with the postprandial rise in serum triglycerides being neither marked nor sustained. Indeed, values differ little from fasting by 7 hours after the fat load. On the other hand, the normotriglyceridemic patients with HyperapoB responded differently in that their plasma triglyceride rose higher; but even more strikingly, this increase was sustained so that at 7 hours this group's levels remained double their fasting levels. Although within the normal range, the fasting plasma triglyceride levels in the patients with HyperapoB were significantly higher than the controls, a finding that is to be expected because increased VLDL synthesis is characteristic of the syndrome.[25] The fat load then, in effect, amplified these differences so they could be examined in greater detail and with greater confidence.

This persistent increase in plasma triglycerides, in turn, appears mainly due to a difference between the two groups in metabolism of Sf > 400 lipoproteins. At 7 hours, in the HyperapoB group, the Sf > 400 triglyceride concentration was substantial, while in the normal group it was virtually nil. Further, many of the HyperapoB patients had significant quantities of Sf > 400 triglyceride even in the fasting sample, a finding we have observed previously in other patients with hyperapobetalipoproteinemia.[14]

Compared to changes in chylomicron levels, there are much less data on the response of VLDL to an oral fat load because of the difficulty in distinguishing between chylomicron remnants and VLDL. In this study, as in others,[26, 27]

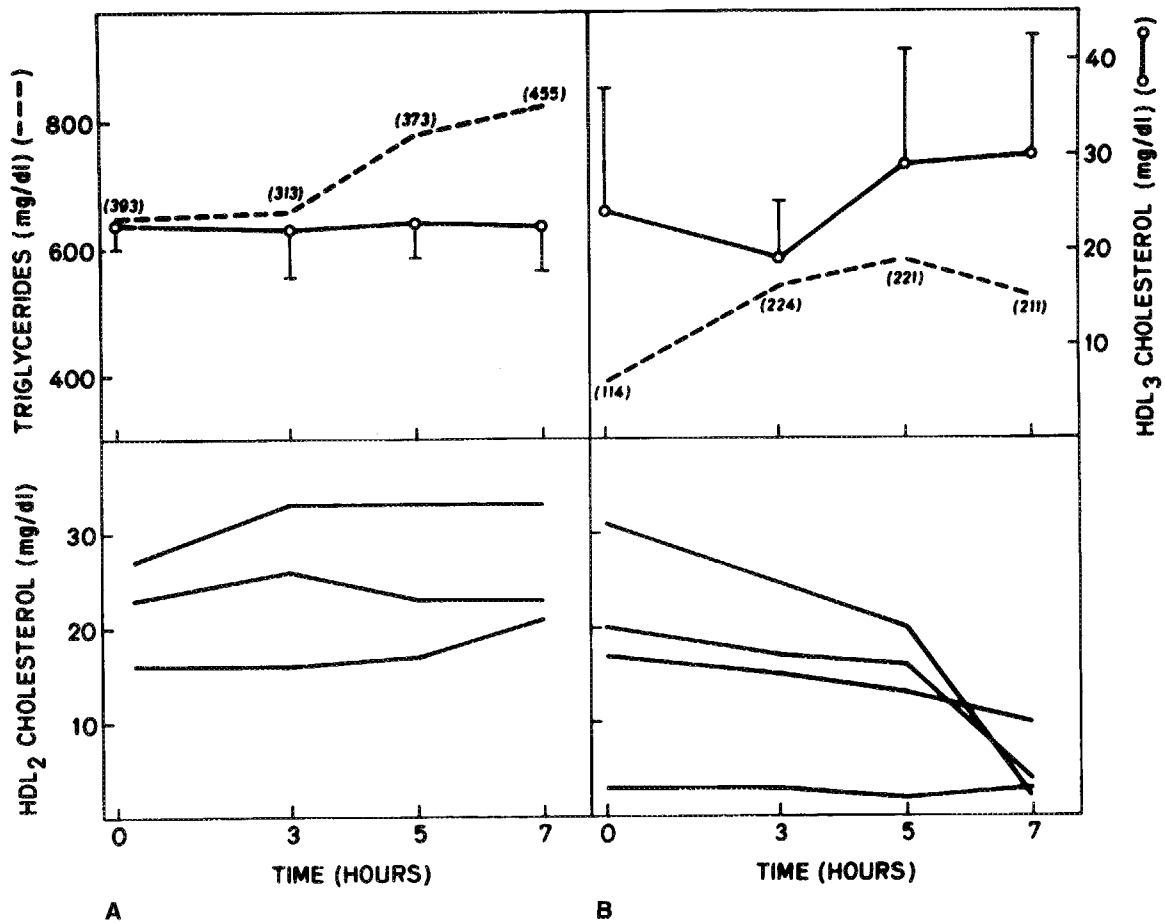

Figure 8. Serial changes after an oral fat load in hypertriglyceridemic normal apo B patients **(A)** and hypertriglyceridemic HyperapoB patients **(B)**. o = HDL_3 cholesterol mean ± SD. Dashed line = plasma triglyceride mean (SD in brackets). Solid line = individual results for HDL_2 cholesterol determinations.

Sf 20–400 triglyceride levels did increase after the fat load. Although it is likely that most chylomicron remnants are removed before they enter this density range,[28] some overlap certainly exists.[27] Similarly, a portion of the Sf > 400 lipoproteins, particularly during the postabsorptive period, might be of hepatic origin.

To overcome the ambiguity inherent in triglyceride measurements, B100 was estimated at Sf > 20, the presumption being that triglyceride-rich lipoproteins of hepatic origin are so identified.[29] Sf > 20 B100 levels did increase in both groups, an increase that could be due to reduced VLDL clearance in the face of continuing hepatic production, perhaps because chylomicrons compete for the same removal pathway,[30] or alternatively, to increased VLDL synthesis stimulated by the fat load. With respect to the measurement of B100, we have shown previously that the B100 monoclonal antibody used in this study can separate B48 and B100 VLDL in Type III[31] and Type IV dyslipoproteinemia.[32] However, it must be appreciated that immunoreactivity can be affected by lipoprotein size or lipid load,[32] and consequently, it is possible that the increases in Sf > 20 B100 levels might be underestimated. Nevertheless, at a minimum, the present data indicate that VLDL B100 levels did increase in both groups in the postprandial period.

The decrease in HDL_2 cholesterol in the HyperapoB group is also of interest. Ingestion of fat initiates a complicated sequence of interactions between chylomicrons and HDL with, at first, the transfer of apoprotein to the newly formed triglyceride-rich particles,[34] and later, after hydrolysis proceeds, the return of lipids and apoproteins to HDL.[35] In addition, it is also known that cholesterol ester and triglyceride exchange between HDL and the triglyceride-rich lipoproteins and that these exchanges are mediated by specific transfer proteins.[36] For the most part, however, while previous studies have shown an increase in protein and phospholipid content in HDL, little change, and certainly no decrease, in cholesterol content has been observed in HDL or its subclasses.[34, 37–39] The exception — other than the present observations — is a preliminary report by Patsch and co-workers[40] who also noted a decrease in HDL_2 cholesterol following a fat load, the degree of which appeared to be related to the extent of postprandial hypertriglyceridemia.

In this regard, it is important to note again that, although within the normal range, the plasma triglyceride levels in the HyperapoB group were certainly higher than in the controls, raising the possibility that the decrease in HDL_2 cholesterol after the fat load might be only a function of plasma triglyceride and not directly related to the syndrome of HyperapoB. The studies in the hypertriglyceridemic patients, however, would argue against this since HDL_2 cholesterol did drop in the hypertriglyceridemic HyperapoB group but not in the others with normal plasma LDL apo B levels.

The lowered HDL cholesterol levels that have been associated with premature coronary artery disease are usually attributed to defective cholesterol transport from peripheral tissues to the liver. This explanation may well be correct, but the present results suggest that it is possible that HDL cholesterol — and in particular HDL_2 cholesterol — may be reduced as a consequence of impaired metabolism of the triglyceride-rich lipoproteins. Further, the present findings of hypertriglyceridemia 7 hours after a fat load in patients with normal fasting triglyceride levels recall the report of deGennes and his colleagues[41] who noted that the same phenomenon was frequently found in normotriglyceridemic patients with premature coronary artery disease.

HyperapoB was first defined as an abnormality of LDL metabolism;[1] subsequent studies showed the increased LDL apo B level in HyperapoB to be due to overproduction of VLDL apo B.[25] The present study now suggests that chylomicron metabolism and HDL_2 metabolism — at least under the conditions in this study — may also be abnormal in this syndrome. Whether these findings are due to a single or to multiple, but unconnected, abnormalities remains to be shown. Further, it remains to be determined whether these faults are extra- or intracellular.

Thus, even though considerable further work must be done, the present results appear important in at least two respects: first, they extend the range of observations that must be explained and linked if possible. Second, they suggest an alternative approach to the traditional lipoprotein risk factor analysis. That is, the impact of plasma lipoproteins on the risk of coronary artery disease has been analyzed statistically as if they were independently regulated with chylomicrons, VLDL, LDL, and HDL all considered to be separate. The present results suggest that, at least in certain instances, they may not be. Thus, the measurement of plasma LDL apo B, which in the first instance led to the recognition of the syndrome HyperapoB, may now lead to the recognition of metabolic relationships previously unrecognized among the plasma lipoproteins.

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Index Terms: hyperapobetalipoproteinemia • oral fat load • HDL cholesterol • hypertriglyceridemia • apolipoprotein B